Interpretation of Statistical Tables from ER/PR Database
DRAFT: January 28, 2008

1. Introduction

This note provides a summary interpretation of the statistical tables from the NLCHI ER/PR Database. The tables address clinical issues only. Communications data will be forthcoming.

Throughout this report, references are made to original data from Eastern Health. It is important to bear in mind, however, that the data represents patients from all regions of the province and that not all of the steps in ER/PR testing take place in the Eastern Health laboratory. For example, tissue extraction and fixation occur at many sites throughout the province before transport to the laboratory, and post-laboratory interpretation and reporting by pathologists occur at many sites as well. Eastern Health collected and reported data on the retesting process for all patients starting in 2005, and therefore the data against which the NLCHI database can be compared belongs to Eastern Health.

2. Total Cases

Eastern Health reported to the public on December 11, 2006 that there were 939 patients retested at Mount Sinai. This number was also reported to the Minister of Health and Community Services on November 23, 2006, to the court in affidavits, and to the media and public throughout the period in 2007 leading up to the appointment of the Commission.

The 939 total was explained by Eastern Health as containing all patients who had an ER/PR negative test result performed at Eastern Health between 1997 and August 2005 and subsequently sent to Mount Sinai for retesting. It was acknowledged as well that the total contained some original positives which doctors had specifically asked to be retested.

Using the same definitions, NLCHI found 1016 cases, or 77 greater than the number reported by Eastern Health. It is not possible to explain completely the difference between the old 939 total and the new 1016 total because, as part of the tracking and data management process within Eastern Health, the spreadsheet which originally contained the 939 count was overwritten with updates many times. Therefore, it cannot be known with certainty how many cases, or which cases, were present or absent from the older Eastern Health spreadsheets. However, the general explanations for the new, higher total are:

- Some cases were identified by Eastern Health or self-identified by patients after the initial reporting of 939 in November 2006;

- Some cases of deceased individuals were not forwarded for testing because of a perception in some RHAs that only living patients need be identified;

- The challenges faced by Eastern Health (e.g., multiple information systems from which to identify original ER/PR tests and original test scores; multiple channels for submitting retests to Mount Sinai; lack of an overarching information system to integrate records for all unique patients).

Within the 1016 cases, there are 18 original positives that were sent to to Mount Sinai for retesting. While the original purpose of retesting was focused on negatives, some physicians asked for certain positive results to be retested. If these are removed for analytical purposes, there is a total group of original negatives of 998 that were sent to Mount Sinai.

3. Comparison of Eastern Health's November 23, 2006 Briefing for the Minister with New Database Results.

The briefing for the Minister on November 23, 2006 included a table with 11 categories of results, with total cases adding to 939. Eastern Health's briefing was primarily focused on the re-test outcomes for the 763 patients identified as living. All deceased patients were assigned to a 12th category entitled "deceased", whether or not re-test results on these cases had been received by that date. Eastern Health reported at that time that 176 people were deceased.

The new database shows that, had Eastern Health been linked to the Provincial Mortality Database, it would have identified 295 people as deceased at that time.[1] This variance means that within the group of 763 cases which were deemed to be living on November 23, 2006, approximately 650 were actually living.[2]

The key comparisons between the Eastern Health table (November 23, 2006) and the new database are as follows:

1. Eastern reported 341 living pateints as "confirmed negative", whereas the new database shows 367 living patients confirmed negative;[3]
2. Eastern reported 213 living patients who had test results that converted from negative to positive but for various reasons had no change in treatment

[1] A year later, in late 2007, the number of deceased grew to (320) people.

[2] This finding gives rise to the question of how Eastern Health could have reported this result if they had been in contact with all patients who were retested This question will be explored further when the database results on communications are known.

[3] The definition of "negative" between 1997 and 2000 uses a cut-off score of 30, and after 2000 it uses a cutoff score of 10. This approach is consistent with the letter (September 6, 2005) from Dr. Cook to lab directors and Medical Directors throughout the province in which instructions were given for the selection of samples for retesting at Mount Sinai. It is also consistent with Dr. Khalifa's proposed cutoff as communicated in his letter to pathologists on February 16, 2998.

recommendation. The new database contains 195 living patients with this outcome.

3. Eastern reported that 104 living patients had a change in test results and required treatment change. The new database found 98 such cases.

Other than the identification of the number of deceased, it cannot be concluded that the Eastern Health table contained errors. The original Eastern Health data cannot be fully verified because the spreadsheets no longer exist to determine which cases were in each of the categories of the table on November 23, 2006. The absence of an auditable trail of records and spreadsheets is a shortcoming of the data management process.

4. Time frame for Retesting

The date that samples were sent to Mount Sinai can be determined for most of the cases. There are 192 cases where the date of testing cannot be determined from existing records. Out of the remaining cases, 88% were sent in 2005, 1% were sent in 2006 and 10% were sent in 2007.

The reason why there was an increase in cases in 2007 was the identification of some deceased that had been originally omitted due to confusion over "inclusion criteria", the inclusion of cases between January and May 1997 over which it was initially unclear whether they were supposed to be retested, and the identification of additional cases that should have been sent in 2005.

Number of Cases by Year of Original Test

The number of original negative ER/PR cases which were retested at Mount Sinai was highest between 1998 and 2002. The volume of tests curtailed substantially in 2004 and 2005.

Table A: Number of Original ER/PR Cases and Tests by year.

Year	Number of Cases	Percentage	Number of Tests	Percentage
1997	63	6.3	61	6.1
1998	159	14.0	140	14.0
1999	167	14.9	150	15.0
2000	195	18.4	182	18.2
2001	151	14.1	142	14.2
2002	157	14.8	147	14.7
2003	110	9.9	98	9.8
2004	61	5.4	54	5.4
2005	28	2.1	24	2.4
Total	1091	100.0	998	100.0

Source: NLCHI Patient Listing and Communication Events- ER/PR Retesting Report (2007)

5. Positivity Rates

The positivity rate is a readily accessible measure of whether a laboratory is producing results within expected ranges. In its initial internal assessment (July 2005) Eastern Health said that the normal range for positivity was 50-85%. Later, in a media briefing on December 11, 2006, Eastern said that the literature suggests that about 75% of breast cancers are estrogen-receptor –positive..... In June of 2007, Eastern reported its positivity rate as "65% from 1997-2005.....". In an affidavit by Dr. Allen Gown, he stated that he had been advised that the seven year average was 74% ER-positivity. Upon review of the generic data given to him by Eastern Health it appeared that the ER positivity rate was in the range of 65-75% for breast cancers analyzed during the time the DAKO instrument was used.

It is important to make some methodological points about this table.

- First, the number of original negative tests (the numerator – column 1) was gathered by NLCHI using criteria for inclusion, plus measures to ensure the exclusion of any ER/PR cases performed for a reason other than breast cancer, any duplicate records and any data entry mistakes.
- Second, the total number of ER/PR tests performed by Eastern (the denominator – column 2) was provided by the Eastern Health. To the extent that there may be cases in the total count that should be excluded, this would make the positivity rate lower. If there were any reasons why cases were missed in the total count, a correction for this factor would make the positivity rate higher.
- Third, some of the retest samples were not the same paraffin blocks that were used to produce the original slides. The number of instances where this happened is not known, but believed to be a minority of the tests, and it is uncertain whether the effect would be to increase, decrease or cause no change in the positivity rate.
- Fourth, between 1997 and 2005 there were 49 negative cases (54 tests) which were subsequently identified as DCIS. These samples have been excluded from both the original tests and the Mount Sinai results because DCIS patients are not normally recommended for Tamoxifen and consequently are not normally sent for ER/PR testing. It remains uncertain whether there are additional DCIS cases within the approximately 2000 positive tests that should be removed if they could be identified.
- Fifth, there are a number of tests (37 in Table B) which could not be interpreted for inclusion. The exclusion of these tests, and the exclusion of DCIS noted above, from both the number of original negatives and the number of total tests, slightly increase the positivity rate.
- Finally, if it is assumed that all laboratories produce a small proportion of false positives, it can be assumed that a small proportion of the 397 tests (column 4) which changed from negative to positive are actually true negatives. This factor, if a true value were known, would make the positivity rate lower.

Table B: Positivity Rate for ER/PR Testing (Original and Adjusted), by Year

Year	[1] # of Original Negative Tests	[2] # of ER/PR Tests done by Eastern*	[3] Original Positivity Rate	[4] Converted Negative to Positive (Based on ≤30 (1997-2000) and ≤10 (2001-2005))	[5] Adjusted Positivity Rate
1997	56	130	56.9	17	70.0
1998	142	201	29.4	55	56.7
1999	158	351	55.0	67	74.1
2000	180	355	49.3	66	67.9
2001	136	359	62.1	70	81.6
2002	149	336	55.7	77	78.6
2003	97	360	73.1	35	82.8
2004	59	393	85.0	10	87.5
2005	23	204	88.7	0	88.7
97-05	1000	2689	62.8	397	77.6
97,99-05	858	2488	65.5	342	79.3
97,99-02	679	1531	55.6	297	75.0

*Data in this column was compiled by the Laboratory Division, Eastern Health. The 1998 number is being further evaluated for accuracy.
Source: Calculated from data provided in NLCHI Patient Listing and Communication Events- ER/PR Retesting Report (2007)

A comparison of the positivity rates during this period with those from the literature is necessary to evaluate the data. One of the difficulties in doing a comparison is that most studies use a consistent 10% cutoff rate for assessing positivity. Eastern Health used this cutoff after 2001, but the rate was 30% before 2001. NLCHI produced tables to adjust for this factor. Table C below summarizes the original and adjusted positivity rates at the variable cutoff rate (30% before 2001 and 10% from 2001-2005), and at the 1%, 10% and 30% cutoff levels.

Table C: Positivity Rate for Original ER/PR Testing, by Cutoff Point, by Year				
Year	Variable Rate	<1%	<10%	<30%
1997	56.9	64.4	56.9	56.9
1998	29.4	47.0	36.3	29.4
1999	55.0	70.7	60.3	55.1
2000	49.3	64.2	53.8	49.3
2001	62.1	70.5	62.1	61.8
2002	55.7	64.4	56.0	55.5
2003	73.1	80.7	73.1	72.7
2004	85.0	87.3	85.0	84.8
2005	88.7	90.3	88.7	88.7
97-05	62.8	72.2	64.7	62.7
97,99-05	65.5	74.2	67.0	65.4
97,99-02	55.6	67.3	58.0	55.6

Another issue with this approach to assessing the retest results is that the original purpose of the retesting process was patient care, not controlled research. Nonetheless, the retest group represents the complete set of negative ER/PR cases between 1997 and 2005 and therefore is unbiased for Newfoundland and Labrador. The characteristics of the Newfoundland and Labrador population could vary from the characteristics of study groups in the literature, but this issue has not been verified one way or another.

6. Changes in ER/PR Scores after Retesting

Eastern Health had a panel of physicians examine most of the retests which had a changed result from Mount Sinai. This process allowed for an expert opinion to be rendered regarding each case, and a valid conclusion drawn on whether a change (i.e., from clinically negative to clinically positive and vice versa), had actually occurred. However, given that not all changed results were examined by the panel, another method is needed to calculate the total rate of changed results between Eastern Health tests and Mount Sinai tests.

Given that the results of the pathology reports, in the main, are reported as a quantitative score between 1 and 100, it is possible to calculate the rate of change from negative to positive for the whole retest group, notwithstanding the determinations of the tumour panel. This approach uses straight mathematics, not clinical judgment, and is not to be regarded as a substitute for the work of the tumour panel. In particular, the change rate in the test results is not an indicator of the proportion of patients who should have received alternate treatment. It is important to bear in mind that only 34% of the changed results as reported by Eastern Health to the Minister on November 23, 2006 needed a change in treatment. Although the NLCHI database includes different numbers than Eastern

Health's report, the general principle would likely remain the same. Despite these cautions, the tables below are a useful way to examine technical aspects of the ER/PR test.

One of the complications in calculating the extent of change in results is how to define negative and positive. Eastern Health states that prior to 2001 the definition of negative was less than 30 and positive was 30 or more. In 2001 the cutoff score was changed to 10, to take into account emerging evidence regarding the benefits of adjuvant therapy like Tamoxifen. Therefore, one way to analyze the data is to classify a "change" according to the cutoff in effect when the original test was done. For example, if a test done in 1998 was 5, and it changed to 25 when retested, it would not be classified as a change because it did not cross the cutoff point of 30. Alternatively, if the same original test with a score of 5 was done in 2002, and the retest score was also 25, it would be classified as a change. This approach has the shortcoming that the actual utilization of these cutoff rates by pathologists is not known and may have varied from physician to physician, but this issue cannot be quantified. The results are presented in Table D.

Table D: Change Rates of Original Negative ER/PR Tests as Compared to Mount Sinai Results, by Year

(Based on ≤30 (1997-2000) and ≤10 (2001-2005)

Year	Confirmed Negatives	Converted Negative to Positive	Change Rate as % of Negatives	Change Rate as % of Total Tests
1997	39	17	30.4	13.1
1998	87	55	38.7	27.4
1999	91	67	42.4	19.1
2000	114	66	36.7	18.6
2001	66	70	51.5	19.5
2002	72	77	51.7	22.9
2003	62	35	36.1	9.7
2004	49	10	16.9	2.5
2005	23	0	0.0	0.0
97-05	603	397	39.7	14.8
97,99-05	516	342	39.9	13.7
97,99-02	382	297	43.7	19.4

Another approach to classification would be to use the same cutoff for the whole period – i.e., either 1, 10 or 30%. Using a cutoff of 10, the example used above would be classified as a change. Using a cutoff of 30, the example above would not be a change. By using a standardized approach, the goal is not to reach a clinical conclusion, but rather to reach a conclusion about the technical aspects of the test. Table E shows the percentage of changes for the four methods noted above (variable cutoff, 1%, 10% and 30%).

Table E: Change Rates of Original Negative ER/PR Tests as Compared to Mount Sinai Results, by Year				
Year	Variable Rate	<1%	<10%	<30%
1997	30.4	27.7	37.5	30.4
1998	38.7	45.8	43.8	38.7
1999	42.4	60.2	56.5	42.0
2000	36.7	45.3	42.3	36.7
2001	51.5	50.5	51.5	39.9
2002	51.7	58.3	51.4	42.7
2003	36.1	37.1	36.1	22.2
2004	16.9	20.0	16.9	13.3
2005	0.0	10.0	0.0	0.0
97-05	39.7	45.7	43.8	35.1
97,99-05	39.9	45.7	43.8	34.5
97,99-02	43.7	50.9	49.0	39.4

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Change Rate by Region

Using the variable cutoff method, the change rates for the province and the four regions are included in Table F.

Table F: Change Rates (Variable Cutoff) by Year and Region Data to be Updated					
Time Period of Original Test	Province	Eastern	Central	Western	Lab/Gren
1997	29.8	25.8	28.6	50.0	0.0
1998	44.3	39.4	56.7	43.8	33.3
1999	54.4	56.4	37.5	68.4	60.0
2000	42.1	34.7	46.9	50.0	83.3
2001	52.2	58.6	36.8	47.4	40.0
2002	54.2	57.8	45.5	50.0	50.0
2003	34.5	39.2	29.4	21.4	50.0
2004	18.0	8.0	42.9	12.5	0.0
2005	0.0	0.0	0.0	0.0	0.0
Total B	43.5	43.4	42.5	43.9	48.5

Source: NLCHI Patient Listing and Communication Events- ER/PR Retesting Report (2007)

Define change rate

On average for the whole period, the regions are not substantially different from the provincial average, except for Labrador/Grenfell at 48.5%, although it is not clear whether this is a concern due to low volumes from that region. There is no obvious pattern of results when each region is examined on a year by year basis.

[Insert new tables with uniform cutoff rates plus assessment of those tables.]

7. Changes by Site

The new database shows that the average percentage of changes by site was 40 percent. In other words, 4 out of every 10 original negative results converted to positive. Most sites were close to or below this average. The two sites with the highest change rate were Clarenville (53%) and Labrador/Grenfell (49%). Given the small number of cases in both areas (15 and 37, respectively), it is not obvious whether there was any problem with pre- or post -analytic factors in these sites.

fixation + interpretation.

Table G: Database Retest Results; Number of Changes (Variable Cutoff) by Site (Total B) (To be updated)

Site	Number of Conversions	Total Unique Retests	%
HSC	47	136	0.35
St. Clare's	117	290	0.40
Grace	27	74	0.36
Carbonear	27	68	0.40
Clarenville	8	15	0.53
Grand Falls	53	122	0.43
Gander	28	74	0.38
Western	69	174	0.40
Lab/Grenfell	18	37	0.49
Total	394	990	0.40

Source: NLCHI Patient Listing and Communication Events- ER/PR Retesting Report

Addendum

Variations between Reported Data and NLCHI Database

1. Positivity Rate

The May 10, 2007 document filed by Eastern Health with the Court contained data on total ER/PR tests conducted between 1997 and 2005, along with the total number of negatives in each year. Dr. Hutton, in a separate filing, used the data to calculate positivity and negativity rates. In December 2007 Eastern Health was asked by government to revisit the total number of tests in 1998 given that the number (147) appeared to be quite low when compared to the number of negative cases in the NLCHI database (139). In January 2008 Eastern Health provided a new number for 1998 (218), but the Department has again asked for a further review because the number still appears to be low compared to other years. The following table provides data on the above points:

Year	May 10, 2007 data from Eastern Health		May 16, 2007 data from Dr. Hutton		January 2008 Revised Data from Eastern Health
	Total Tests	Negatives	Pos%	Neg%	Total Tests
1997	137	57	58	42	137
1998	147	76	48	52	218
1999	360	126	68	32	360
2000	370	170	54	46	370
2001	374	173	60	40	374
2002	344	147	58	42	344
2003	373	89	76	24	373
2004 DAKO	109	16	85	15	109
2004 Ventana	381	41	90	10	381
2005	114	19	84	16	114
Total	2709	914			2780

Given the changed result for 1998, the data and calculations before the court will need to be amended.

2. False Negatives

In the May 10, 2007 affidavit, Eastern Health states that there were 330 changed patient results based on Mount Sinai testing. Thirteen of these changes were due to a change in the definition of positive, four had a change in diagnosis and 4 were retro-converters (positive to negative). Therefore, 309 changes was the net number of false negatives

(306 from DAKO and 3 from Ventana). It is noteworthy that this number does not include any deceased cases. The total number of changed cases in the NLCHI database is 377. In May 2007, Dr. Hutton estimated the total number of false negatives (DAKO results only) for living and deceased by inferring that the proportion of false negatives from the deceased results to date would be the same as among the deceased not then tested. His total was 366 false negatives.

Dr. Hutton then used this number of patients to calculate the number of false negatives as a proportion of total tests (2214 tests on DAKO, meaning that 16.6% were false negatives). The mixing of patient and test data is not a sound practice because some patients had more than one test sent to Mount Sinai for retesting.

Part of this problem is corrected in the August 3, 2007 document filed by Eastern Health with the Court which included the number of false negatives based on the Mount Sinai test results, not patient results (using the variable cutoff approach). The explanation of the methodology in the affidavit would indicate that it excluded incorrect diagnoses, cases affected by changed definitions, and cases which were originally positive. This approach means that it is consistent with the NLCHI approach. Eastern Health does not explain whether it has included test results for the 105 deceased patients who had been retested up to that point in time, but the similarity in total count with NLCHI indicates that they are included. The number of false negatives from Eastern Health's affidavit and from NLCHI's database are as follows:

	1997	1998	1999	2000	2001	2002	2003	2004	2005	Total
Eastern	16	51	71	49	61	71	39	12	2	372
NLCHI	17	53	62	65	65	76	30	9	0	377